

LINARIENONE, A NEW CIS-CLERODANE-TYPE DITERPENE  
FROM THE SUBTERRANEAN PART OF LINARIA JAPONICA MIQ.

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During the course of studies on the chemical constituents of Linaria japonica Miq. (unran in Japanese, Scrophulariaceae), we have first elucidated the structure of linarioside (1),<sup>1)</sup> which was isolated from the water-soluble portion of epigeous and subterranean parts of the plant and was the first example of chlorine-containing iridoid-glucoside, and afterwards, we have established the structure of a cis-clerodane-type diterpene dialdehyde named linaridial (2),<sup>2)</sup> which was obtained as the major component of the ether extractive of fresh subterranean part. In a continuing study on the ether-soluble portion, we have recently isolated another new cis-clerodane-type diterpene designated as linarienone (3) (ca. 1% from the ether ext.) whose structure elucidation is the subject of this communication.

Linarienone (3), C<sub>27</sub>H<sub>40</sub>O<sub>5</sub>,<sup>3)</sup> oil, [ $\alpha$ ]<sub>D</sub> +30° (CHCl<sub>3</sub>), possesses an angelate group [UV  $\lambda$  max (EtOH): 219 nm ( $\epsilon$  13000); IR (CCl<sub>4</sub>, cm<sup>-1</sup>): 1718; PMR (CCl<sub>4</sub>,  $\delta$ ): 1.96 (3H, d, J= 7 Hz), 1.91 (3H, br.s), 5.96 (1H, q-like, J= 7); liberation of angelic acid on alkaline hydrolysis], a  $\beta,\beta$ -disubstituted  $\alpha,\beta$ -unsaturated six-membered ketone [UV: 245 nm ( $\epsilon$  11000); IR (CCl<sub>4</sub>): 1666, 1625 (sh); PMR (CCl<sub>4</sub>): 5.70 (1H, br.s,  $W_{h/2}$  = 3 Hz)], and an acetoxyl group [IR (CCl<sub>4</sub>): 1737]. On treatment with 1% NaOMe-MeOH at room temp., 3 was converted to desacetyl-linarienone (4), C<sub>25</sub>H<sub>38</sub>O<sub>4</sub>, while on treatment with 10% NaOH-MeOH-benzene under reflux, 3 was hydrolyzed to give desdiacyl-linarienone (5), C<sub>20</sub>H<sub>30</sub>O<sub>2</sub>, and angelic acid.

The detailed PMR examinations including spin-decoupling experiments of 3, 4, and 5, have shown the presence of partial structures, i, ii, and iii in linarienone (3) (some PMR data in CDCl<sub>3</sub> of 3 and 4 (with \*) being given). In the mass spectra of 3, 4, and 5, is observed a

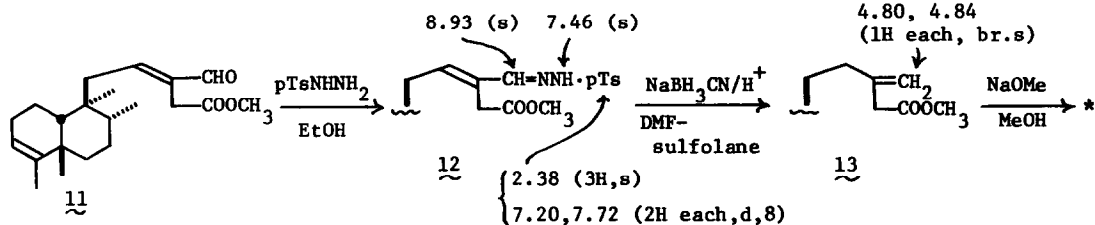
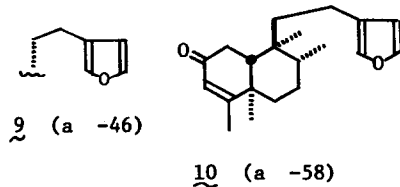
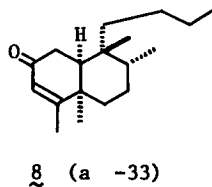
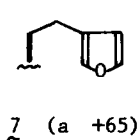
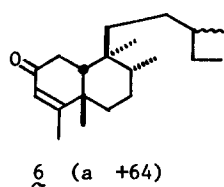
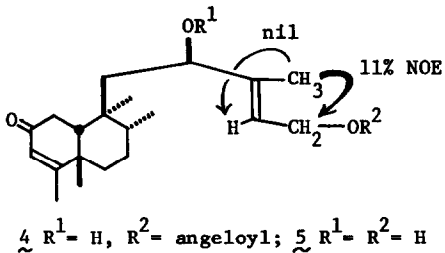
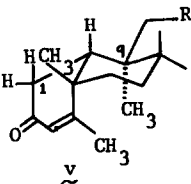
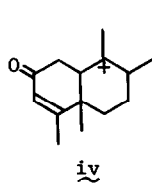
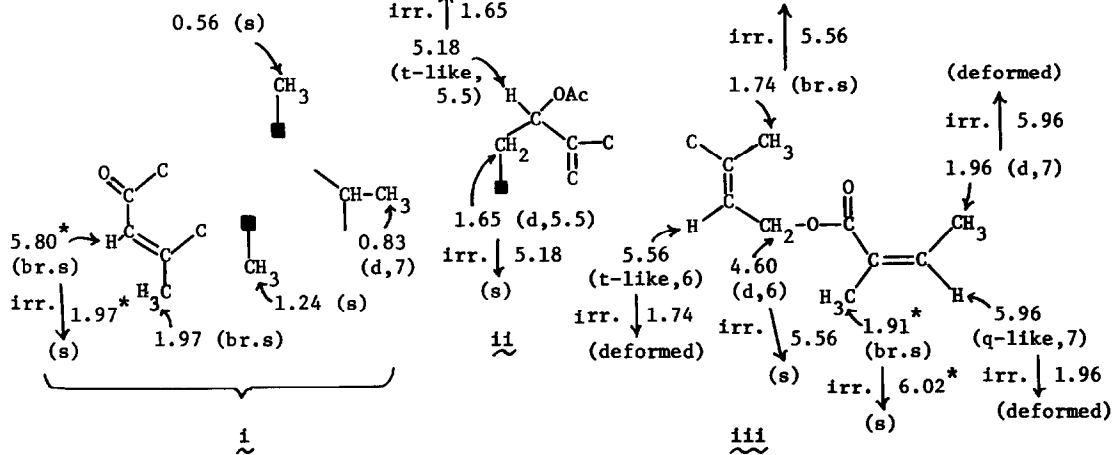
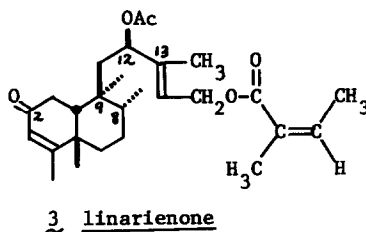
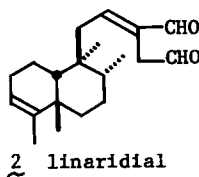
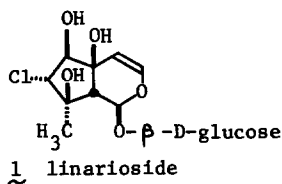
prominent ion peak of  $C_{14}H_{21}O$  ( $m/e$  205) which, in combination with the partial structure i and with the presence of  $\alpha$ -methylene protons of carbonyl in 3 [main signals at  $\delta$ 2.42 (1H, br.s) and  $\delta$ 2.52 (1H, br.d,  $J_{obs.} = 6$  Hz)], is assigned iv (cf. v).

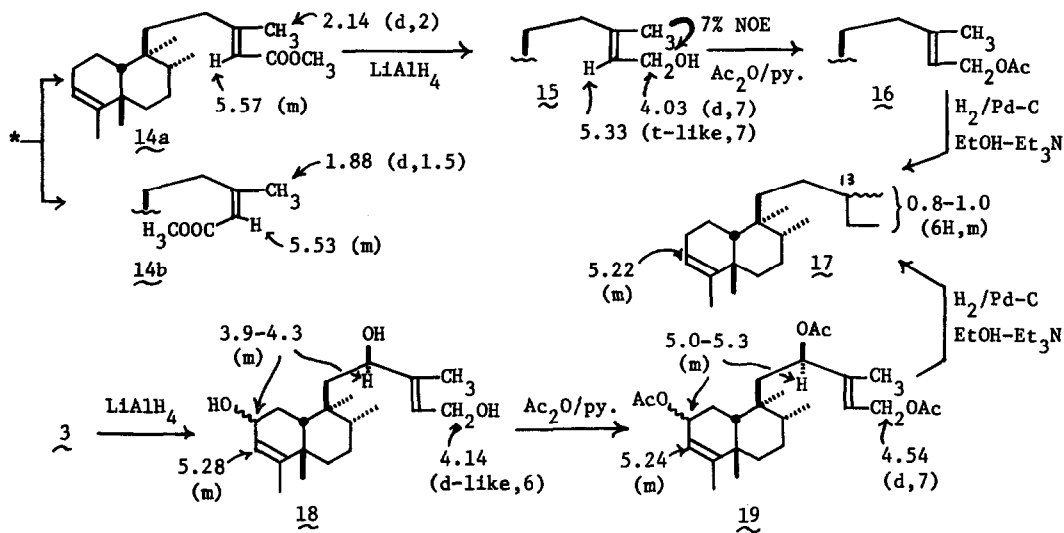
Based on the above evidence along with the molecular composition of linarienone, if a cis-clerodane-type skeleton is presumed, the plane structure of linarienone could be expressed as 3 (without stereochemistry).

In order to clarify at first the absolute configuration at C-12 and the geometry of  $\Delta^{13}$ , desacetyl-linarienone (4) was examined by the Horeau's method,<sup>4)</sup> and it has been shown that the configuration at C-12 in 4 has been determined to be R ( $[\alpha]_D$  of  $\alpha$ -phenylbutyric acid recovered in two experiments were  $+2.7^\circ$  and  $+3.4^\circ$  (benzene), respectively). Next, the NOE examinations of 4 were undertaken and an 11% enhancement was observed between 13- $CH_3$  and 14- $CH_2O$ -angeloyl while no NOE between 13- $CH_3$  and 14-H, thus the geometry of  $\Delta^{13}$  being determined to be E (as seen in 3, 4, and 5).

As for the stereostructure of decaline part in linarienone (3), the following evidence is suggestive (except the configuration at C-8). Thus, by comparison of CD and ORD data of 3 ( $a$  +53), 4 ( $a$  +52), and 5 ( $a$  +67) with those of five clerodane-type derivatives (6,<sup>5)</sup> 7,<sup>6)</sup> 8,<sup>7)</sup> 9,<sup>8)</sup> and 10<sup>9)</sup>, the presence of a  $5\beta$ -methyl-cis-clerodane structure having a 3-en-2-one moiety in linarienone (3) has been demonstrated. Based on Dreiding model examinations of 3 in relation to chemical shift values of 5- $CH_3$  ( $\delta$  1.24), 8- $CH_3$  (0.83), and 9- $CH_3$  (0.56) and to the coupling pattern of 1-H<sub>2</sub> (vide supra), an assumption has been made that a stereostructure v (steroidal) is contained in 3 in which 9- $CH_3$  is shielded by a carbonyl at C-2.

Finally, the structure of linarienone (3) has been established on the basis of following conversion from both linaridial (2) and linarienone (3) to a common cis-clerodane-type hydrocarbon (17). The ester-aldehyde (11)<sup>2)</sup> prepared from 2 was derivated to a tosylhydrazone (12), which, on reduction with  $NaBH_3CN/HCl/DMF$ -sulfolane,<sup>10)</sup> was converted to 13,  $C_{21}H_{34}O_2$ . On treatment with  $NaOMe-MeOH$ , 13 was isomerized to a 4:1 mixture of 14a and 14b (both  $C_{21}H_{34}O_2$ ). The major E isomer (14a) was subjected to  $LiAlH_4$  reduction to give 15,  $C_{20}H_{34}O$ , the geometry of  $\Delta^{13}$  being supported by NOE examinations. The monoacetate 16,  $C_{22}H_{36}O_2$ , prepared from 15 was hydrogenated with  $H_2/Pd-C/EtOH-Et_3N$  (hydrogenolysis accompanied) to give an aimed hydrocarbon 17,  $C_{20}H_{36}$ ,  $[\alpha]_D +14.8^\circ$  ( $CHCl_3$ ) (presumably a 1:1 mixture on the C-13 configuration), as an unstable oil. The structures of all compounds (11  $\rightarrow$  17) in the reaction pathway are well supported by their physical properties (some PMR data given in the scheme).





On the other hand, linarienone (3) was converted to the hydrocarbon (17) via the following pathway.  $\text{LiAlH}_4$  reduction of 3 gave a triol (18), which, on acetylation (giving 19) followed by hydrogenation and hydrogenolysis as for 16, was transformed to a hydrocarbon being identical to 17 obtained above by TLC, IR,  $[\alpha]_D$ , GLC, and mass spectra.

Consequently, the structure of linarienone including the absolute configuration has been established as 3. Linarienone (3) seems to be the second example of *cis*-clerodane-type di-terpene found in the scrophulariaceous plant (the first one was linaridial (2)).

#### References and Footnote

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